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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO.
09/679,664	10/03/2000	Thomas M. Stormann	072827-1801	7662

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/679,664	STORMAN ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *12-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment B, filed 11/27/02, has been entered into the record.

B. Claims 1-41 were pending in the application. In Amendment B, Applicants added new claims 42-46. Claims 12-41 were withdrawn as being drawn to a non-elected invention. Therefore, claims 1-46 are pending and claims 1-11 and 42-46 are the subject of this Office Action.

C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

D. The Examiner appreciates Applicants' submission a full set of the claims under consideration.

2. Oath/Declaration

A. All objections to the Oath/Declaration has been withdrawn since Applicants have submitted a new Oath with the correct spelling of "Stormann" and have initialed all changes made the Oath.

3. Specification

A. All objections to the specification have been withdrawn in view of Applicants' amendments.

4. Claims Objections

A. The objection to claim 1 regarding the use of a colon after the term "comprising" has been withdrawn. Though it is pointed out to Applicants that claims 11 and 42 both use a colon after the term "comprising" as it does make clear that a selected group is to follow.

B. The objection to claims 5, 7, 8 and 11 have been withdrawn in view of Applicants' amendments to the claims.

5. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 1-11 remain rejected and new claims 42-46 are also rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 3-5 of the Office Action dated 7/22/02. Applicants argue that the artisan would recognize that, based on the amino acid sequence differences between CaR, mGluR and $GABA_B$ receptors from different sources, that the various domains of these receptors and thus of the claimed fusion proteins can encompass such variations and remain functional and that domains of

"at least 10 residues" can easily be tested for function. Applicants also argue that examples of these fusion proteins are claimed.

These arguments have been considered, but are not deemed persuasive. The domains of these receptors are hundreds of amino acids in length, ranging from approximately 200 residues for the intracellular region to 600 residues for the extracellular regions. Again, the term "substantially" has been defined in the specification as having at least 40% similarity to a given polypeptide region. Therefore, these domains could have hundreds of potential residues either added, deleted, inserted, or substituted. In addition, the claims recite that the intracellular domain can have as few as 10 residues and new claims 44-46 can have as few as 90% of 50 residues identical to the wild-type. Again, this means that this domain could have hundreds of potential residues either added, deleted, inserted, or substituted. Applicants have not identified which residues are required to maintain the function of these domains, of the overall fusion protein. Therefore, not only is the breadth of these claims excessive, but, there is only minimal guidance and working examples of any fusion constructs (Figures 8 and 15). Furthermore, it is not predictable to one of ordinary skill in the art what residues can be altered while still maintaining the functional characteristics of the individual domains, as well as the entire fusion protein. Applicants have added a limitation to claim 1 regarding the lack of an interaction of the intracellular domain with the G protein. However, this limitation is, itself, respectfully, insufficient to enable the invention.

Therefore, in summary, the breadth of the claims is excessive due to the large number of possible alterations that can be made to each of the extracellular, transmembrane and intracellular domains for each of three possible receptors. In addition, there is only minimal guidance and working examples of fusion constructs. For these reasons, along with the lack of predictability to one of ordinary skill in the art as to what residues can be altered while still maintaining the functional characteristics of the individual domains, as well as the entire fusion protein, the Examiner holds that undue experimentation would be required to practice the invention as claimed.

6. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, have been withdrawn in view of Applicants' arguments, or amendments to the claims. However, a new rejection under 35 USC 112, second paragraph, appears below.

B. Claim 45 is rejected under 35 USC 112, second paragraph, since it recites "MRluR." It is believed that this claim intended to recite "MGluR."

7. Claim Rejections - 35 USC § 103

A. Claims 1-11 remain rejected and new claims 42-46 are also rejected under 35 USC 103 as being unpatentable over Fuller et al., in view of Bertin et al., further in view of Negulescu et al., further in view of Kaupmann et al. and further in view of Rock et al. for the reasons already of record on pages 6-9 of the Office Action dated 7/22/02. Applicants argue that the Examiner has not shown that there would have been a reasonable expectation of success in making the present invention. Applicant has amended claim 1 to recite that the intracellular domain of the wild-type receptor does not interact with said G-protein and asserts that it would not have been obvious to try these fusion proteins. Applicant argues that the only fusion receptor cited in the Bertin et al. reference involved a fusion between a wild-type receptor and a Gsα with which the receptor normally interacts and that there is no indication that a fusion should be made comprising the intracellular domain of one of the claimed receptors.

Applicant also argues that Bertin et al. propose precoupling a receptor to a naturally interacting G-protein subunit and that there is no teaching that this procedure could be used with G proteins which do not normally interact with the receptor. This argument has been considered, but is not deemed persuasive. Regardless of whether or not the G protein normally interacts with the receptor, the physical procedure of linking the G protein to the receptor would be the same and there would be an identical expectation of success in coupling any G protein to any G protein-coupled receptor using the techniques taught by Bertin et al.

Applicant states that Fuller et al. do not teach fusion proteins, but rather chimeric proteins, as they include domains from different receptors. However, since the present claims recite receptors which include domains from different receptors, it is not clear how these proteins differ from those of Fuller et al. since Fuller et al. teach combining domains from both CaRs and mGluRs, as is claimed by the present invention. The argument that the only fusion receptor cited in the Bertin et al. reference involved a fusion between a wild-type receptor and a Gsα with which the receptor normally interacts and that there is no indication that a fusion should be made comprising the intracellular domain of one of the claimed receptors has also been considered, but is not deemed persuasive. Negulescu et al. teaches that promiscuous G proteins exist and can couple to various G protein-coupled receptors (GPCRs). These G-proteins (e.g. Gα15 or Gα16) couple to GPCRs which normally couple to G-proteins of other families. Therefore, the intracellular domains of the fusion proteins of the present invention would not be expected to interact with these promiscuous G proteins in a wild-type cell.

One of ordinary skill in the art would have been motivated to produce a G-protein fusion protein comprising the promiscuous G-proteins, Gα15 or Gα16 since the production of chimeric G-protein

coupled receptors usually alters the function of these receptors as compared to wild-type and, though, these fusion (chimeric) receptors may be expressed on the cell surface of a transfected cell, it would not be clear if these receptors were functional. Due to the substitution of various domains in order to produce a chimeric receptor, the ability of the carboxyl tail of the chimera, unlike the wild-type receptor, may lose its ability to associate and activate G-proteins. Therefore, even though this protein may still retain function, it would not be known to the artisan since the affinity for the "normal" G-protein, or its ability to couple to downstream effectors, may be lost. Therefore, the use of a promiscuous G-protein would produce a high probability of success that if the G-protein chimera was functionally active, that this activity would be detected and further characterization of this chimera could continue. In fact, Applicant even claims (e.g. claim 5) that Gα15 or Gα16 can be used in the present invention, showing that these proteins meet the added limitation of claim 1.

Though Applicant argues that there is no reason given by Negulescu et al. to produce the claimed receptors, as there is no reason to link the GPCRs of the invention to a G protein, as taught by Bertin et al., the motivation is seen when all of these references are taken together. CaR/mGluR fusion (chimeric) receptors were known and were known to be functional at the time of the present invention (Fuller et al.). Promiscuous G proteins were also known (Negulescu et al.). These promiscuous G proteins were known to couple to a wide variety of GPCRs, and it would be expected that they would be able to couple to fusion proteins of GPCRs. Therefore, due to the ability of promiscuous G proteins to couple to a wide variety of GPCRs, the artisan would have been motivated to use these proteins to determine the functionality of a fusion protein, since these G proteins would allow for the maximum flexibility of the system and the best chance to identify functional fusion proteins. Given the teachings of Bertin et al. that it is desirable to link the G protein to the GPCR, the artisan would have been motivated to perform this procedure for the present invention to optimize the conditions in order to produce the best chance of identifying these functional fusion proteins.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
February 24, 2003

Gary L. Kunz

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